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# Treatment of hepatitis C infection among Egyptian hemodialysis patients: the dream becomes a reality

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## Abstract

**Background and aims** New direct-acting antiviral drugs have become the corner-stone treatment for HCV infection: they show promising results with accepted side-effects and low dropout rates. One of the available regimens is paritaprevir/ombitasvir/ritonavir (PTV/OMV/RTV). Our aim was to study the efficacy and safety of this drug regimen among HCV-positive hemodialysis patients.

**Methods** This prospective single-center study was performed in the Urology and Nephrology Center, Mansoura University, Egypt. Ninety-six maintenance hemodialysis patients were screened for HCV antibodies. Positive results were found in 46 patients (47.9%). HCV PCR was assessed in all HCV-antibody-positive patients; positive results were found positive for 38 (82%); all patients were HCV genotype 4. Four patients were excluded due to advanced liver cirrhosis, liver malignancy, or metastatic breast cancer. Thirty-four patients were prescribed PTV/OMV/RTV for 3 months to treat HCV.

**Results** Mean age was 43.2 ± 11.9 years. Most patients were male (67.6%). There was a rapid response to treatment: HCV PCR became negative by 4 weeks after starting treatment. By 12 and 24 weeks post-DAA therapy, there was a sustained viral response (SVR 12, SVR 24) in 100% of patients with improved liver-enzyme levels.

**Conclusion** The PTV/OMV/RTV regimen was safe and effectively treated Egyptian HCV-positive genotype-4 hemodialysis patients.

**Keywords** Antiviral agents · Chronic hemodialysis · Chronic hepatitis C · Drug interaction · DAA therapy

## Introduction

Egypt has the highest prevalence of HCV worldwide. In 2008, the Egyptian Demographic Health Survey (EDHS) estimated the prevalence of HCV antibodies and HCV RNA among those aged 15–59 years to be 14.7 and 9.8%, respectively, based on a large national study [1]. Among Egyptians infected with HCV, more than 90% are genotype 4; the remainder are genotype 1 [2].

Chronic kidney disease always impacts negatively on the treatment of chronic hepatitis because of poor drug tolerance, a higher prevalence of side-effects, and the complexities of adapting drug dosages [3].

Conventional alpha interferon (IFN) was one of the available treatments for HCV among hemodialysis patients with a sustained virological response (SVR) of 20–71%. Treatment-related withdrawal rates were 0–53%. Many clinical trials were included in Fabrizi et al.; meta-analysis that studied

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treatment of HCV infected dialysis patients with alpha-IFN. SVR rates ranged from 20 to 70% [4]. Pegylated alpha-IFN has been another treatment for HCV RNA positive hemodialysis with a SVR rate of 0–79% and treatment-related withdrawal rates of 0–56%. Gordon et al. performed a systematic review in which in 20 clinical trials, patients were treated with alpha-IFN which were compared to five clinical trials where patients were given pegylated alpha-IFN. They found comparable SVR rates among both groups (41–37%) and overall comparable results between them [5].

After the development of new direct-acting antivirals (DAAs), the treatment of HCV was much improved with fewer side-effects compared to IFN therapy. The problem with first-generation DAAs was the need to combine them with alpha-interferon, with the associated side-effects and numerous drug–drug interactions. In addition, some major second-generation DAAs (e.g., sofosbuvir) undergo major renal clearance, thus making them unsuitable for use when the estimated glomerular-filtration rate (eGFR) is < 30 mL/min [6].

The minimal renal clearance of the recently available combined therapy of paritaprevir/ombitasvir/ritonavir (PTV/OMV/RTV) means that this is mostly metabolized in the liver, and so, this therapy is not contraindicated for patients with chronic renal failure [7].

The European Association for the Study of the Liver (EASL) guidelines 2016 recommend that patients with severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$) or with end-stage renal disease and receiving hemodialysis without an indication for kidney transplantation infected with HCV genotype 4 should be treated with the combination of ritonavir (RTV)-boosted paritaprevir (PTV) and ombitasvir (OBV) for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is > 10 g/dL at baseline, or with the combination of grazoprevir and elbasvir for 12 weeks without ribavirin [8].

The aim of this study was to determine the safety and efficacy of the paritaprevir/ombitasvir/ritonavir (PTV/OMV/RTV) regimen given to a relatively large sample of genotype-4 hemodialysis patients and to compare the data with those in other studies, in a real-life setting. In addition, we evaluated the role of adding ribavirin to this regimen, i.e., does ribavirin affects outcomes; is it possible to dispense with the use of ribavirin? We also asked if removal of dasabuvir from the PTV/OMV/RTV regimen affected outcomes?

## Patients and methods

This prospective, single-center study was conducted at the Urology and Nephrology Center, Mansoura University, Egypt. The 96 chronic hemodialysis-dependent patients that attended our clinic were screened for HCV antibodies using the chemiluminescent micro-particle immunoassay technique (Architect set, Abbot). Positive results were found in 46 cases (47.9%). HCV PCR was performed using HCV RNA TaqMan Real Time PCR test (Ampiprep/COBAS TaqMan 48 set, Roche). A value of < 15 IU/L was considered to be negative. For patients that were HCV-antibody positive; HCV RNA positive results were obtained for 38, i.e., 82%; the remainder had spontaneous clearance of HCV RNA. All patients were already HCV seropositive before hemodialysis was started, transmitted either via blood transfusions or while receiving treatment for bilharziasis. Four patients were excluded because of advanced liver cirrhosis, liver malignancy, or metastatic breast cancer. Thus, 34 patients were included in this study. Figure 1 represents the flowchart of the study population.

All 34 patients received 12 weeks of DAAs that included 25 mg OBV/150 mg PTV/100 mg RTV, administered orally once daily. Ribavirin (200 mg/day) was added for 10 patients that had baseline hemoglobin of > 10 g/dL, a white blood-cell count of > 2000/$mm^3$, and a platelets count of > 100,000/$mm^3$. The follow-up after treatment completion was 6 months.

Before initiating treatment, the patients were thoroughly evaluated, which included a clinical examination. Laboratory investigations included quantitative HCV RNA PCR, liver-enzyme levels, i.e., aspartate (AST) and alanine (ALT) aminotransferases, serum bilirubin, serum albumin, alpha fetoprotein level, antinuclear autoantibodies (ANA), and thyroid-stimulating hormone (TSH). Abdominal ultrasonography was conducted to exclude malignancy. Any adverse

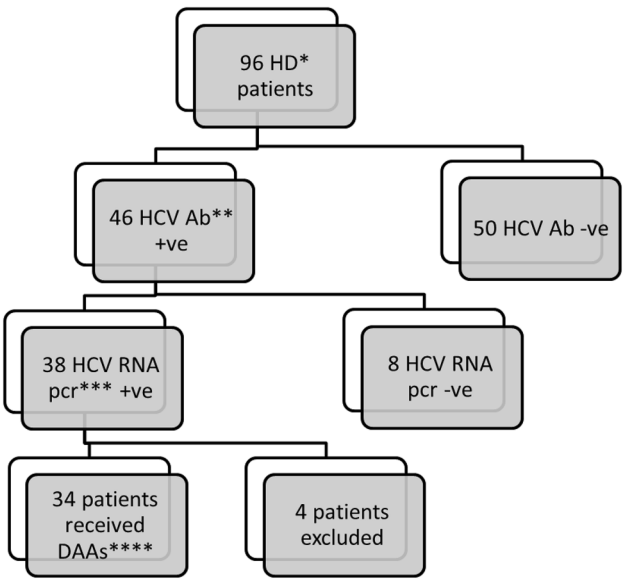


**Fig. 1** Flowchart of the study population. **HD* hemodialysis, ***HCV Ab* hepatitis C virus antibody, ****HCV RNA pcr* HCV RNA polymerase chain reaction, *****DAA* direct-acting antivirals

events (AEs) were evaluated at each visit [weeks (W) 0, 4, 8, and 12]. Clinical laboratory testing was performed during the treatment period and at 1, 3, and 6 months after completing treatment.

All procedures were conducted in accordance with the ethical standards of the committee on human experimentation at our institution (Mansoura University Hospital).

Oral informed consent was obtained from every subject.

### Statistical analyses

All data were tabulated in an SPSS sheet. Descriptive measures were used for demographic and pretreatment data. Repeated-measures ANOVA tests for parametric data and the Freidman test for non-parametric data were conducted to compare the laboratory findings before, during, and after treatment. When comparing ribavirin compared to non-ribavirin groups, Fisher's exact test was used for nominal and ordinal data and Student's *t* test was used for continuous data. A result was considered statistically significant if the *p* value was $\leq 0.05$.

## Results

Most patients were male (23 male and 11 female). Ages ranged from 30 to 50 years (Table 1). Body-mass index was $23.8 \pm 4.6$ kg/m$^2$ (range 18.5–24.9). Ischemic heart disease and hypertension were the most common medical disorders: 38.2% and 35.3% of cases, respectively. No patient had cancer. Most had normal thyroid function based on TSH levels; only two suffered from hyperthyroidism. Two patients had been previously treated for HBV and HBV DNA had become negative. Two patients had previously received alpha-interferon to treat HCV. Jaundice and ascites were not detected in any patient during clinical examinations, but four patients suffered from chronic lower limb edema. No patient had a history of previous hepatic encephalopathy. All patients were HCV genotype-4. Liver and spleen ultrasound findings, fibroscan results, and the clinical conditions associated with hepatic disease and HCV genotypes are listed in Table 2.

**Table 1** Demographic data and associated medical disorders

| Variable | Hemodialysis patients |
|---|---|
| Age (mean ± SD) (years) | 43.2 ± 11.9 |
| Gender: no. (%) | |
| Male | 23 (67.6%) |
| Female | 11 (22.4%) |
| Body-mass index (mean ± SD) (kg/m$^2$) | 23.8 ± 4.6 |
| Previously treated by alpha-interferon, no. (%) | 2 (5.8%) |
| Comorbidities: no. (%) | |
| Hypertension | 12/34 (35.3%) |
| Diabetes mellitus | 5/34 (14.7%) |
| Ischemic heart disease | 13/34 (38.2%) |
| HBV co-infection | 2/34 (5.8%) |
| Original kidney disease: no. (%) | |
| Glomerulonephritis | 7/34 (20.6%) |
| Lupus nephritis | 3/34 (8.5%) |
| APKD | 2/34 (5.9%) |
| Obstructive uropathy | 4/34 (11.8%) |
| Others | 18/34 (53.3%) |

*HBV* hepatitis B virus, *APKD* autosomal dominant polycystic kidney disease

### Efficacy

Overall, there was a rapid virological response (RVR) to treatment: HCV PCR became negative after 4 weeks of treatment in all patients and an SVR was obtained at 12 and 24 weeks in 33 of 34 patients. DAA treatment was not suspended for any patient and all completed the 3-month continuous treatment course. One patient had a relapse

**Table 2** Clinical conditions associated with hepatic disease

| Variable | 34 hemodialysis patients, no. (%) |
|---|---|
| CHILD score [no. (%)] | |
| CHILD A | 32 (94.2%) |
| CHILD B | 1 (2.9%) |
| CHILD C | 1 (2.9%) |
| Fibroscan | |
| F0 | 15 (44.1) |
| F1 | 14 (41.2) |
| F2 | 5 (14.7) |
| HCV PCR [no. (%)] | |
| Weak (< 100,000) | 9 (26.5%) |
| Moderate (100,000—800,000) | 13 (38.2%) |
| High (> 800,000) | 12 (35.3%) |
| Liver ultrasound [no. (%)] | |
| Normal | 27 (79.4%) |
| Enlarged | 7 (20.6%) |
| Spleen ultrasound [no. (%)] | |
| Normal | 25 (73.5%) |
| Mild enlargement | 6 (17.6%) |
| Moderate enlargement | 2 (5.8%) |
| Marked enlargement | 1 (2.9%) |
| HCV genotypes [no. (%)] | |
| 1 | 0 |
| 2 | 0 |
| 3 | 0 |
| 4 | 34 (100%) |

after an initial RVR. This patient was aged 67 years and had been previously treated with alpha-interferon (there was HCV RNA clearance during therapy but a subsequent HCV RNA relapse after alpha-interferon cessation). Before starting DAA therapy, a liver fibroscan was F2 and the Child–Pugh score was B. Regarding this relapse, HCV PCR was negative at 1 month after completing treatment but became positive at 2 months later. The patient developed lower limb edema and ascites at 3 months after completing treatment. Laboratory investigations showed an increase in ALT from 32 to 67 IU/L, of AST from 30 to 69 IU/L, serum albumin decreased from 3.6 to 2.4 g/dL, and HCV PCR became positive at 4300 IU/L. HCV PCR was repeated at 1 month later and was then 8450 IU/L The patient underwent daily dialysis and ultrafiltration with the aim of improving ascites and lower limb edema, and received IV albumin and ursodeoxycholic acid. The patient was then clinically improved and liver-enzyme levels returned to within normal values by 1 month later, but HCV PCR remained positive. This patient is the only patient that showed hepatic decompensation as a potential adverse event of DAA therapy.

Overall, there was significant improvement in liver-enzyme levels, especially of ALT and serum bilirubin (Table 3). Otherwise, there was no statistically significant differences regarding other laboratory parameters, including AST, total cholesterol, prothrombin time (data not shown), and hematological parameters (Table 3) between before, during, and after DAA treatment.

## Ribavirin added to DAA therapy compared to no ribavirin

Table 4 shows the demographic and baseline characteristics of the two subgroups. There were no statistically significant differences across the groups regarding age, gender, body-mass index, ALT level, Child–Pugh score, fibroscan, liver ultrasound, spleen ultrasound, or HCV RNA viral load. Baseline hemoglobin was slightly but not significantly greater among those receiving ribavirin. However, doses of erythropoietin-stimulating agents (ESA) were significantly elevated among those receiving ribavirin at baseline ($p = 0.05$). All patients from both groups achieved a RVR, and 12 and 24 week SVR was 100% for the ribavirin group and 95.8% for the non-ribavirin group ($p =$ ns). ALT levels decreased significantly after DAA therapy, i.e., $27.18 \pm 9.38$ vs. $62 \pm 41.06$ IU/L ($p = 0.016$) in the ribavirin group and $22.7 \pm 9.29$ vs. $51.36 \pm 21.07$ IU/L ($p = 0.001$) in the non-ribavirin group. One relapse and hepatic decompensation case occurred in the non-ribavirin group (see above). Worsening of anemia was statistically more frequent in the ribavirin group (70%) compared to 17.5% of patients in the non-ribavirin group ($p = 0.001$). Accordingly, ESA doses at 4 weeks after starting DAA treatment were significantly higher in the ribavirin group than in the non-ribavirin group ($p = 0.0016$). In the ribavirin group, ESA doses at 4 weeks after starting DAA treatment were slightly higher than prior to treatment ($11{,}100 \pm 4012$ vs. $9000 \pm 4472$ IU; $p = 0.2$) (see

**Table 3** Efficacy and safety parameters during and after DAA therapy

| Variable | Before starting treatment | 4 weeks after starting treatment | 4 weeks after completing treatment | 12 weeks after completing treatment (SVR 12) | 24 weeks after completing treatment (SVR 24) | *p* value |
|---|---|---|---|---|---|---|
| Serum bilirubin mg/dL (mean ± SD) | 0.41 ± 0.13 | 0.46 ± 0.20 | 0.41 ± 0.13 | 0.38 ± 0.13 | 0.34 ± 0.12 | 0.012 |
| Serum albumin g/dL (mean ± SD) | 3.75 ± 0.33 | 3.76 ± 0.37 | 3.78 ± 0.29 | 3.85 ± 0.37 | 3.72 ± 0.34 | 0.73 |
| ALT, IU/L med (min, max) | 17 (4174) | 9 (1, 35) | 9 (5, 43) | 8 (2, 30) | 5 (2, 21) | 0.001 |
| Hemoglobin, g/dL (mean ± SD) | 11.01 ± 1.38 | 10.81 ± 1.35 | 10.45 ± 1.26 | 10.71 ± 1.25 | 10.56 ± 1.74 | 0.175 |
| Erythropoietin dose, IU/week | 8294.11 ± 4093.81 | 9264.7 ± 3544.59 | 8411.76 ± 3798.86 | 8520.66 ± 3587.36 | 8431.78 ± 3689.21 | 0.0005 |
| White blood count $*10^3/mm^3$ (mean ± SD) | 5.57 ± 1.69 | 6.14 ± 1.74 | 6.07 ± 1.54 | 5.98 ± 1.75 | 5.96 ± 1.86 | 0.08 |
| Platelets $\times 10^3/mm^2$ (mean ± SD) | 181 ± 78.1 | 194.4 ± 88.5 | 195 ± 82.18 | 189 ± 84.97 | 191.44 ± 63.4 | 0.320 |
| HCV PCR (IU/L) $\times 10^3$ (mean ± SD) | 283 ± 76 | Negative | Negative in 33/34 patients | Negative in 33/34 patients | Negative in 33/34 patients | |

*DAA* direct-acting antivirals, *ALT* alanine aminotransferase, *SVR* sustained virological response, *PCR* polymerase chain reaction, *SD* standard deviation, *IU* international unit, *HCV* hepatitis C virus

**Table 4** Patients baseline characteristics in the ribavirin-treated group vs. the non-ribavirin group

| | Ribavirin group (10 patients), no. (%) | No ribavirin group (24 patients), no. (%) | *p* value |
|---|---|---|---|
| Age (years), mean ± SD | 40.28 ± 10.9 | 43.1 ± 11.2 | 0.5 |
| Gender (male), no. (%) | 7 (70) | 16 (66.67) | 0.85 |
| Body-mass index, mean ± SD | 23.4 ± 4.3 | 22.6 ± 3.5 | 0.6 |
| Previously treated with interferon (yes), no. (%) | 0 | 2 (8.3) | 0.347 |
| Hepatitis B co-infection (yes), no. (%) | 1 [10] | 1 (4.2) | 0.51 |
| Hypertension (yes), no. (%) | 3 (30) | 9 (37.5) | 0.677 |
| Diabetes (yes), no. (%) | 3 (30) | 2 (8.4) | 0.104 |
| Previous kidney transplantation, no. (%) | 6 (60) | 15 (62.5) | 0.891 |
| CHILD score [no (%)] | | | |
| CHILD A | 8 (80) | 24 (100%) | 0.512 |
| CHILD B | 1 [10] | 0 | |
| CHILD C | 1 [10] | 0 | |
| Fibroscan [no. (%)] | | | |
| F0 | 5 (50) | 10 | |
| F1 | 4 (40) | 10 | |
| F2 | 1 [10] | 4 | |
| HCV PCR [no. (%)] | | | |
| Weak | 1 [10] | 8 (33.3) | 0.190 |
| Moderate | 6 (60) | 7 (29.2) | |
| High | 3 (30) | 9 (37.5) | |
| Liver US [no. (%)] | | | |
| Normal | 8 (80) | 18 (75) | 0.32 |
| Enlarged | 2 (20) | 6 (25) | |
| Cirrhotic | 0 | 0 | |
| Spleen US [no. (%)] | | | |
| Normal | 8 (80) | 16 | 0.278 |
| Mild enlargement | 0 | 6 | |
| Moderate enlargement | 2 (20) | 1 | |
| Marked enlargement | 0 | 0 | |
| Bilirubin (mg/dL), mean ± SD | 0.39 ± 0.13 | 0.41 ± 0.12 | 0.583 |
| Albumin (mg/dL), mean ± SD | 3.64 ± 0.33 | 3.88 ± 0.33 | 0.233 |
| ALT (IU/L), mean ± SD | 62 ± 41.06 | 51.36 ± 21.07 | 0.45 |
| Hemoglobin (g/dL), mean ± SD | 11.19 ± 1.98 | 10.92 ± 1.08 | 0.623 |
| ESA dose (IU/week), mean ± SD | 9000 ± 4472 | 5958.3 ± 3950 | 0.05 |

*SD* standard deviation, *HCV* hepatitis C virus, *PCR* polymerase chain reaction, *US* ultrasound, *ALT* alanine aminotransferase, *ESA* erythropoietin-stimulating agents, *IU* international unit

Table 5). Although ESA doses were increased by 1 month after starting treatment and ribavirin dose was decreased to 200 mg every other day, hemoglobin levels in five patients did not improve and, thus, ribavirin was stopped during the third month of treatment.

One-year follow-up: 1 year after from completing treatment, four patients died (one due to arrhythmia, one due to sepsis, and two due to persistent intra-dialytic hypotension). They all died with negative HCV PCR and good liver function. The relapser patient did not receive treatment till now as grazoprevir/elbasvir regimen is not available for free in Egypt. The remaining 29 patients are still HCV RNA negative with normal liver-function tests and no signs of hepatocarcinoma. Finally, none of them showed any signs of hepatic decompensation.

## Anemia during DAA therapy

Anemia (i.e., hemoglobin < 11.5 g/dL) worsened in 10 (29.4%) of 34 patients; in every patient iron indices (serum ferritin, transferrin saturation test, and total iron-binding capacity) were assessed. Patients with a transferrin saturation test of < 20% (3 patients) received IV iron (100 mg after every hemodialysis for ten sessions, and then 100 mg/week). In addition, these patients received increased doses of ESAs (Table 3). Of these ten patients, seven were maintained

**Table 5** Add-on ribavirin therapy: outcomes

| | Ribavirin group (10 patients), no. (%) | No ribavirin group (24 patients), no. (%) | *p* value |
|---|---|---|---|
| RVR, no. (%) | 10 (100) | 24 (100) | |
| 12-Week SVR, no. (%) | 10 (100) | 23 (95.8) | 1 |
| 24-Week SVR, no. (%) | 10 (100) | 23 (95.8) | 1 |
| SVR after 48 weeks from completing treatment, no. (%) | 10 (100) | 23 (95.8) | 1 |
| Relapse, no. (%) | 0 | 1 (4.2) | 1 |
| Hepatic decompensation, no. (%) | 0 | 1 (4.2) | 1 |
| Worsening of anemia, no. (%) | 7 (70) | 3 (17.5) | 0.0019 |
| ALT after completing treatment | 27.18 ± 9.38 | 22.7 ± 9.29 | 0.24 |
| Hemoglobin 4 weeks after starting treatment, mean ± SD | 10.81 ± 1.48 | 10.81 ± 1.33 | 0.996 |
| Hemoglobin 4 weeks after completing treatment, mean ± SD | 10.28 ± 1.50 | 10.52 ± 1.18 | 0.615 |
| ESA dose 4 weeks from starting treatment, mean ± SD | 11,100 ± 4012 | 6223.3 ± 3950 | 0.0016 |
| ESA dose 4 weeks from completing treatment, mean ± SD | 8400 ± 3949 | 5846.3 ± 3950 | 0.11 |
| Drug interruption | 5 (50%) (RBV only) | 0 | 0.00009 |

*RVR* rapid virological response, *SVR* sustained virological response, *ALT* alanine transferase, *SD* standard deviation, *ESA* erythropoietin-stimulating agents, *RBV* ribavirin

on ribavirin and dose was decreased to 200 mg every other day (during the second month of treatment). Ribavirin was then stopped (during the third month of treatment) for five patients where hemoglobin did then not increase, even though ESA was increased.

Other adverse events included dizziness (three cases), fatigue (two cases), and bone aches (five cases).

### Drug interactions

Before DAA therapy, 18 patients were receiving amlodipine therapy for hypertension. Due to the potential interaction between DAAs and amlodipine, the latter was stopped and replaced with another anti-hypertensive drug. One patient received carbamazepine (200 mg/day) for peripheral neuropathy: he was also asked to stop this prior to starting DAA treatment; however, he continued taking this without informing us. Fortunately, he did not experience a virologic failure or a virological relapse, and we did not follow-up the concentrations of carbamazepine. All patients were advised to seek our advice before starting any new medication while receiving DAA therapy to avoid any drug interactions. In addition, no patient on dialysis due to a previous allograft failure was taking immunosuppressive medications.

## Discussion

The 12-week treatment with paritaprevir/ombitasvir/ritonavir (PTV/OMV/RTV ± RBV) was based on the 2016 EASL guidelines for the treatment of HCV genotype-4 patients undergoing hemodialysis [9].

Our study included 34 hemodialysis patients (68% were male; overall mean age 43 years). All were genotype 4, most were Child–Pugh score A and were F0 or F1 by fibroscan. Most had a normal-sized liver and a normal-to-mildly enlarged spleen (as assessed by ultrasound). All received PTV/OMV/RTV + RBV to 10 patients and PTV/OMV/RTV without RBV to 24 patients. Neither regimen included dasabuvir. We found that this was effective at treating genotype-4 hemodialysis patients, both with or without ribavirin, although including ribavirin was associated with a higher incidence of anemia (70%).

We compared our results to those from six previous reports on DAA therapy given to chronic dialysis patients (Table 6). Most studies, including ours, used a PTV/OMV/RTV ± RBV regimen for 12 weeks. Sato et al. randomized patients for either 12 or 16 weeks of DAA therapy: they reported improved efficacy for the 16-week regimen with higher SVR rates [11]. Suda et al. also evaluated the efficacy of daclatasvir and asunaprevir and found a 95.9% SVR at week 12 [12].

Table 7 summarizes the virological efficacy and side-effects across the six studies. In our study, RVR was achieved in 100% of patients and 12- and 24-week SVRs were achieved in 33 of 34 patients. In addition, there was significant improvement in liver-function tests, i.e., ALT and total bilirubin levels. Similar results were reported by Morisawa et al. in 2017, where most HCV (+) genotype 1b chronic dialysis patients (8/10 patients) achieved rapid eradication of the virus with ritonavir + paritaprevir + ombitasvir therapy [14]. A lower RVR was achieved in 3/6 hemodialysis patients included in Sperl et al.'s study on sofosbuvir/daclatasvir [10]. In contrast,

**Table 6** DAA therapy in chronic dialysis patients: baseline characteristics

| | This report | Sperl et al. [10] | Sato et al. [11] | Akhil et al. [12] | Morisawa et al. [14] | RUBY I (cohorts 1 and 2) [15] | RUBY II [16] |
|---|---|---|---|---|---|---|---|
| No. of patients | 34 | 6 | 171 | 22 | 10 | 68 | 18 |
| Age (years) | > 18 | > 18 | > 18 | > 18 | > 18 | > 18 | > 18 |
| Predominant gender | Male | Equal | Female | Male | Equal | Male | Male |
| HCVPCR (IU/L) | > 100,000 | > 100,000 | > 100,000 | > 100,000 | > 100,000 | > 100,000 | > 100,000 |
| HCV genotype | 4 | 3a | 2a, 2b | 1, 3, 4 | 1b | 1 | 1, 4 |
| Child–Pugh score | A | A and B | A | A | A | A | A |
| Fibroscan | F0, F1 | F1, F4 | | F0-F3 | NA | F0-F4 | F0-F3 |
| Hemoglobin (g/dL) | > 10; add RBV < 10; no RBV | > 10 | > 10 | > 10 | NA | > 10 | > 8 |
| Treatment | OMV/PTV/RTV ± RBV | Sof/Dac | OMV/PTV/RTV | Sof/RBV | OMV/PTV/RTV | OMV/PTV/RTV + RBV | OMV/PTV/RTV No RBV |

*DAA* direct-acting antivirals, *HCV* hepatitis C virus, *PCR* polymerase chain reaction, *IU* international unit, *RBV*, ribavirin *OMV*, ombitasvir *PTV*, paritaprevir, *RTV* ritonavir, *Sof* sofosbuvir, *Dac* daclatasvir

**Table 7** DAA therapy given to chronic dialysis patients: response to therapy and adverse effects

| | This report | Sperl et al. [10] | Sato et al. [11] | Akhil et al. [13] | Morisawa et al. [14] | RUBY I [15] | RUBY II [16] |
|---|---|---|---|---|---|---|---|
| No. of patients | 34 | 6 | 171 (95 continuing) | 22 | 10 | 68 | 18 |
| RVR | 34 | 3 | 84 | 22 | 8 | 65 | 17 |
| 12-SVR | 33/34 | 6/6 | 79/95 | 16/22 | 8 | 65/68 | 17/18 |
| 24-SVR | 33 | NA | NA | NA | 8 | NA | NA |
| Virologic failure during treatment | 0 | 0 | 8 | 3 | 0 | 0 | 0 |
| Relapse | 1 | 0 | 5 | 3 | 0 | 3 | 1 |
| Hepatic decompensation | 1 | 0 | | | 0 | | |
| Anemia (yes) | 10 | 0 | 4 | | 0 | 28 | 0 |
| Drug interruption | 5 (RBV only) | 0 | 3 | 9 | 2 | 2 | 1 |
| Other adverse events | Bony aches | Nausea | Headache, pruritis | | Erythema multiforme, severe drowsiness | Fatigue, nausea | Abdominal pain, nausea, diarrhea |

*DAA* direct-acting antivirals, *RVR* rapid virological response, *SVR* sustained virological response, *ESA* erythropoietin-stimulating agents, *RBV* ribavirin, *NA* not applicable

Akhil et al. reported a 100% RVR with a sofosbuvir/daclatasvir regimen [13].

An SVR was achieved in 33/34 of our cases (97%). This was a higher percentage than reported by Morisawa et al., who reported an 80% SVR with the same drug regimen [14]. Our result was also higher than that reported in the RUBY 1 trial (cohort 1 [8] and cohort 2 [15]) which evaluated a combination of ombitasvir, paritaprevir, ritonavir, plus dasabuvir, with or without ribavirin (RBV), given to 68 genotype-1 infected patients with chronic kidney disease (stage 4 or 5). The RUBY 1 trial found that 90% (65/68 patients) achieved an SVR by week 12 (in intention-to-treat analysis) [15]. However, the RUBY II study reported higher SVRs (94.4%), which is a similar finding to our study [16]. A Japanese study that included non-renal, non-cirrhotic, HCV genotype-2 infected patients that received OBV/PTV/RTV + RBV reported an SVR of 91.5% [11]. In contrast and compared to the sofosbuvir-based regimen in our study, Akhil et al. reported 12-SVR

rates of 72.2% (16/22) [13], whereas Sperl et al. reported a 100% (6/6) 12-week SVR rate for a lower sample size [10].

Liver-function parameters, including serum albumin, ALT, AST, and total bilirubin levels, were assessed at baseline and then monthly during treatment, and then every 3 months after completing treatment. None of our patients had increased liver-enzyme levels. Total bilirubin levels and ALT were significantly improved after completing treatment compared to data collected at baseline. The other liver-function parameters did not change during treatment. Similarly, Morisawa et al. found no change in liver-function parameters during treatment [14]. Sato et al. and Akhil et al. reported that total bilirubin levels were not changed significantly during treatment, remaining within normal ranges; however, they found that serum AST and ALT levels were significantly improved upon completion of treatment compared to baseline data [11, 13].

The adverse events reported in our study included relapse (one case), hepatic decompensation (one case), and anemia (ten cases).

The most serious complication was a relapse. Hepatic decompensation also occurred in one patient in our study (2.9%). The relapse may have been caused by advanced fibrosis. The RUBY I trial reported a 10% relapse rate at 4 weeks after stopping treatment, which was attributed to advanced fibrosis and interruption of ribavirin therapy [15]. Akhil et al.'s study used a sofosbuvir-based regimen and reported a high rate of relapse (6/22; 27.27%), of which three patients had virologic failure from the start [13]. This suggests a higher efficacy of the OMV/PTV/RTV regimen over the sofosbuvir-based regimen for dialysis patients. Sato et al. compared a 12-week regimen to a 16-week regimen of OMV/PTV/RTV: there were 5/47 relapsers in the 12-week group and a total virologic failure in 8/95 [11].

Anemia was a frequent adverse effect (34.2%) in our study and was more frequent in the ribavirin group than in the non-ribavirin group. Anemia required ribavirin dose to be modified to 200 mg every other day and ESA doses were increased. Only two patients in the ribavirin group responded to decreased ribavirin and increased doses of ESA. For the remaining five patients, anemia was not improved and ribavirin needed to be stopped.

In the RUBY 1 trial, anemia was the most common adverse event, but only developed in genotype-1a patients where ribavirin was administered, implying that ribavirin was interrupted at some point during the course of treatment [15]. The RUBY II trial did not report any cases of anemia as they had not included ribavirin in their regimen [16]. Akhil et al. [13] reported that anemia was the most common adverse effect (40.9) and was caused by ribavirin, but all patients except one responded to decreased RBV doses and increased doses of ESA.

The second most common complication in our study was bone ache. Other complications included dizziness, fatigue, and gastrointestinal upsets. Different adverse events (including bone aches, nausea, abdominal pain, and pruritis) have been reported in other studies [10, 11, 13, 15]. The RUBY II trial reported that all included patients developed an SVR with a ribavirin-free ombitasvir/paritaprevir/ritonavir ± dasabuvir regimen, but that a major AE occurred in four patients (22%), including worsening hypertension. Gastroenteritis and pulmonary edema were observed, but were considered to be not related to the drug regimen [16].

In general, all of the AEs in our study were well tolerated and no patient discontinued treatment because of them.

When comparing the ribavirin to non-ribavirin group, efficacy was very similar as nearly all patients achieved an RVR and 12- and 24-week SVRs. The only difference was the frequency of anemia: there was worsening anemia in the ribavirin group, which was accompanied by RBV interruption. When comparing the RUBY I to the RUBY II trial, they reported similar results to us regarding comparisons between ribavirin and no ribavirin [15].

Our study has the advantage focusing on only HCV genotype-4 patients and having a relatively large sample size. We also followed-up patients for at least 1 year after completing the treatment course. The study evaluated the role of adding ribavirin to a PTV/OMV/RTV regimen. We were able to treat all patients without adding dasabuvir.

Some shortcomings of our study are the lack of randomization and unblindness. We were not able to use grazoprevir/elbasvir regimen nor glecaprevir/pibrentasvir, because they were not were available in Egypt at the time which we started this study.

We conclude that, in real life, the paritaprevir/ombitasvir/ritonavir (PTV/OMV/RTV regimen) with or without ribavirin therapy was safe and effectively treated Egyptian HCV-positive genotype-4 hemodialysis patients. At least in our patients, addition of Dasabuvir did not seem necessary. Avoiding ribavirin was associated with fewer adverse events and better tolerability without affecting the efficacy of the therapeutic regimen.

**Author contributions** AYE: wrote the article, HME and YEM: collected the data, AFR and KFE: analyzed the data, ME: followed the patients from hepatology point of view, and HS: was the responsible for laboratory investigations. GMS: afforded the DAAs in help with Egyptian medical insurance. The work was under supervision of MAB and LR: they reviewed and finalized the article.

## Compliance with ethical standards

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